REMARKS

Applicants have cancelled Claims 1-3, 7 and 8 without prejudice to, or disclaimer of, the subject matter contained therein. Applicants maintain that the cancellation of a claim makes no admission as to its patentability and reserve the right to pursue the subject matter of the cancelled claim in this or any other patent application.

Applicants have amended Claims 4, 5, 6 and 14 to delete elements (a)-(d). Claims 4 and 5 are amended to delete the portion of the claim "wherein said isolated nucleic acid encodes a polypeptide that is more highly expressed in normal skin tissue compared to melanoma." Claim 14 is amended to include "or a complement thereof" to amended elements (a)-(c), and the following text "wherein said isolated nucleic acid molecule is suitable for use as a PCR primer, or probe; and wherein said isolated nucleic acid is at least about 20 nucleotides in length." Claim 16 is amended to read "at least about 50 nucleotides in length." Claim 17 is amended to depend from Claim 4. New Claims 21-31 have been added.

Applicants submit that no new matter has been added by the amendments, and that support for the amendments can be found throughout the specification. Support for the amendments to Claim 14 can be found, for example, at paragraphs [0012], [0317], and [0327] of the specification. Support for the amendment to Claim 16 and new Claims 21-25 can be found, for example, at paragraph [0012]. Support for new Claims 26-31 can be found, for example, in the claims as originally filed, and paragraphs [0227] and [0317].

Priority

The Examiner asserts that U.S. Provisional Patent Application Serial No. 60/099,812 does not provide utility/enablement and written description for the claimed polynucleotides. Thus, the Examiner asserts that the application is not entitled to priority based on U.S. Provisional Patent Application Serial No. 60/099,812.

The Examiner further asserts that the application is not entitled to priority based on Example 18 (tumor versus Normal Differential Tissue Expression Distribution) in PCT Application PCT/US00/23328 because the PCT application does not comply with the written description, utility and enablement requirements. The Examiner maintains that the priority date of the present application is its filing date, May 8, 2002.

As indicated in the Amendment and Response to Office Action submitted October 1, 2004, Applicants have previously listed the priority information for the instant application in a Preliminary Amendment mailed September 4, 2002. The preliminary amendment states that the instant application is a continuation of, and claims priority under 35 U.S.C. § 120 to, US Application 10/006867 filed 12/6/2001, which is a continuation of, and claims priority under 35 U.S.C. § 120 to, PCT Application PCT/US00/23328 filed 8/24/2000, with is a continuation-in-part of, and claims priority under 35 U.S.C. § 120 to PCT Application PCT/US00/14042, filed 5/22/2000, which is a continuation-in-part and claims priority under 35 U.S.C. § 120 to, US Application 09/403297 filed 10/18/1999, now abandoned, which is the National Stage filed under 35 U.S.C. § 371 of PCT Application PCT/US99/20111 filed 9/1/1999, which claims priority under 35 U.S.C. § 119 to US Provisional Application 60/099812 filed 9/10/1998.

Applicants submit that for the reasons stated below, the claimed polynucleotides have a credible, substantial, and specific utility. The sequence of SEQ ID NO: 51 was first disclosed in US Provisional Application 60/099812 filed 9/10/1998. The data in Example 18 (Tumor Versus Normal Differential Tissue Expression Distribution), relied on in part for the utility of the claimed polynucleotides, were first disclosed in PCT Application PCT/US00/23328 filed 8/24/2000, on page 93, line 3, through page 96, line 35. Accordingly, Applicants maintain that the present application is entitled to claim priority to US Provisional Application 60/099812 and PCT/US00/23328.

Rejections Under 35 U.S.C. §101

Claims 1-8,11-14 and 16-20 were rejected under 35 U.S.C. 101 on the assertion that the claimed invention is not supported by either a specific, substantial and credible asserted utility or a well established utility. The Examiner asserts that neither the nucleic acid nor the encoded protein have a substantial utility or well-established utility. The Examiner maintains that the data presented in Example 18 are preliminary at best, and cannot be evaluated or repeated independently by the skilled artisan. According to the Examiner, the specification does not set forth the number of independent samples tested, the levels of the nucleic acid or protein in the samples such that the "higher" levels in normal tissue as compared to levels in melanoma was determined to be statistically significant. The Examiner asserts that the specification does not set forth the conditions and the probes used to determine the "levels" of SEQ ID NO:51 in the

sample tested and the skilled artisan would not know under what conditions and using what probes that a difference in expression could be detected. The Examiner maintains that it is not clear if under/overexpression was detected in 1/10 or 10/10 independent samples tested. The Examiner asserts that no levels (relative or absolute) are disclosed in the specification as originally filed. The Examiner also asserts that it is not known in the art, and the specification does not teach if the nucleic acid is involved in causing/suppressing the melanoma.

The Examiner asserts that the nucleic acid encoding the polypeptide has no utility because (1) the nucleic acid of SEQ ID NO:51 per se has no utility and (2) the encoded protein has no utility (i.e. as it relates to the embodiments claiming a nucleic acid encoding a polypeptide). According to the Examiner, the actual biological activity of the encoded polypeptide is not set forth in the art or the specification. The Examiner asserts that Applicants have not measured expression of the polypeptide per se, nor have they demonstrated increased mRNA expression as compared to an appropriately matched tissue control and shown that the difference is statistically relevant for melanoma samples as compared to normal skin. Further, the Examiner asserts that a skilled artisan would not believe the assertion that the level of DNA is correlated with the level of mRNA and corresponding level of encoded polypeptide.

According to the Examiner, the teachings of the specification are limited to an apparently single test using undisclosed probes/primers and conditions and fail to establish qualitative or quantitative measures for mRNA or protein. The Examiner asserts that the specification fails to establish that the expression pattern is statistically significant with multiple independent samples of different patient samples having the same cancer type as compared to normal tissues.

The Examiner asserts that the relied upon utility (decreased nucleic acid/mRNA or protein expression in melanoma as compared to normal skin) specifically requires or constitutes carrying out further research to identify or reasonably confirm a "real world" context of use and as such is therefore not a "substantial utility" (see MPEP 2107.01(1)). The Examiner asserts that Applicants have provided a single analysis of nucleic acid without any relative range for basing a utility of under-expression for the claimed protein(s). According to the Examiner, no levels (relative or absolute) are disclosed. In addition, the Examiner maintains that there is no data regarding protein expression in melanoma and normal skin in the specification. The Examiner asserts that the art shows that DNA copy number, mRNA levels and protein levels are not

inexorably related, in that an increase in one necessarily leads to an increase in all of them. According to the Examiner, transcription levels (mRNA) do not correlate with polypeptide levels and Applicants have not provided any specific role for the lack of the encoded polypeptide in cancer.

The Examiner cites Haynes et al. (1998, Electrophoresis 19:1862-1871), as showing that the protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript. The Examiner also cites the textbook by Lewin as teaching that "... production of RNA cannot be inevitably be equated with production of protein" (page 487, column 2, last paragraph). According to the Examiner, this concept is reconfirmed by a variety of studies such as that evidenced by Gokman-Polar et al (Cancer Research 61:1375-1381, 2001) that indicates the absence of any necessary correlation between increased mRNA levels and increased protein levels. The Examiner cites Pennica et al (PNAS, 95:14717-22, 1998) as showing that there is a lack of correlation between gene amplification and protein expression of the WISP protein and asserts that this teaching in combination with Haynes et al indicates that there is no significant correlation between nucleic acid level and translation. Hu et al. (2003, Journal of Proteome Research 2:405-412) is cited as showing that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. The Examiner acknowledges that Hu shows that, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section).

The Examiner asserts that even if the nucleic acid has a utility as a melanoma tumor marker, the nucleic acid encoding the protein does not have utility because the protein has no utility and it is not known what the protein does or if the level of the PRO1411 protein in melanoma corresponds to transcript level (i.e. if a decreased amount of transcript corresponds to a decreased amount of expressed protein) for reasons made of record. According to the Examiner, it does not necessarily follow that a decrease in transcript levels results in a corresponding decrease in protein expression, such that the polypeptide would be useful diagnostically or as a target for cancer drug development. The Examiner asserts that the cited

references establish that one skilled in the art would not associate DNA copy number, mRNA and protein levels as necessarily reflecting each other.

The Examiner asserts that the first declaration of Dr. Grimaldi merely reiterates the assertion in the specification that since the RNA levels are different then "this indicates that the gene and its corresponding polypeptide and antibodies are useful for diagnostic purposes to screen samples to differentiate between normal and tumor." According to the Examiner, this is not persuasive because it relies upon a tight correlation of RNA production with protein expression. The Examiner maintains that visual detection of nucleic acids is highly subjective and that the grading as + or - or +/- is quantitative. The Examiner further asserts that Applicants have not set forth the evidentiary basis for their assumption that a visual difference relates to an at least 2-fold difference in cDNA or 2 fold difference in protein. According to the Examiner, Applicants have provided no objective evidence that supports this assertion of qualitative and quantitative results. The Examiner also questions the use of pooled samples and asks about the likelihood that a tissue sample from a patient with suspected melanoma would have a lower level of the nucleic acid of SEQ ID NO:51. The Examiner also questions how many samples would be needed and what sensitivity would be needed. The Examiner asks whether the normal tissue would have to be a pooled sample or whether it be from a single individual.

The Examiner also asserts that the second declaration by Dr. Grimaldi (previously submitted as Exhibit 2) is not persuasive. The Examiner cites paragraph 4 of the Declaration, in which mutations in Her2/Neu and chromosomal translocations are discussed, and the statement that "when the chromosomal aberration results in the aberrant expression of mRNA and the corresponding gene product (the polypeptide), as it does in the aforementioned cases, the gene product is a promising target for cancer therapy, for example, by the therapeutic antibody approach." According to the Examiner, the specification provides a mere invitation to experiment, and not a readily available utility. The Examiner also asserts that the therapeutic antibodies in the art rely upon statistically relevant increased polypeptide expression or unique polypeptide expression. According to the Examiner, there is no basis for asserting that therapeutic antibodies would be useful in a scenario where the protein is under-expressed in the tumor. In addition, the Examiner asserts that the PRO1411 gene, unlike Her2/Neu, has not been associated with tumor formation or the development of cancer, nor has it been shown to be

predictive of such. The Examiner also asserts that the statement in paragraph 5 that increased mRNA expression is expected to be associated with increased protein production is Declarant's opinion and is not supported by fact or evidence. The Examiner also asserts that there has been no distinction on the record in general or in the specification as filed between total nucleic acid, which includes chromosomal DNA and mRNA. According to the Examiner, one cannot determine for the data in the specification whether the observed "more highly expressed" is due to mutation, copy number differences or transcription rates.

The Examiner asserts that the Declaration by Dr. Polakis is unpersuasive. According to the Examiner, the Declaration does not provide data such that the examiner can independently draw conclusions, or provide any objective evidence. The Examiner asserts that only Dr. Polakis' conclusions are provided in the declaration. According to the Examiner, Applicants have presented no objective evidence with respect to the statistical relevance or levels of nucleic acids, nucleic acids encoding polypeptides or polypeptides. According to the Examiner, there is no evidentiary support for Dr. Polakis' statement that it remains a central dogma in molecular biology that increased mRNA levels a re predictive of corresponding increased levels of the encoded polypeptide and one of skill in the art would not believe this to be true. Citing Hu et al., the Examiner states that the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue.

The Examiner asserts that the Orntoft et al., Hyman et al., and Pollack et al. references submitted by the Applicants were unpersuasive. The Examiner maintains that Orntoft et al did not look at gene amplification, mRNA levels and polypeptide levels from a single gene at a time. According to the Examiner, Orntoft et al concentrated on regions of chromosome with strong gains of chromosomal material containing clusters of genes (page 40). The Examiner asserts that this analysis was not done for the PRO1411 genes. According to the Examiner, it is not clear whether or not PRO1411 is in a gene cluster in a region of the chromosome that is highly amplified.

The Examiner asserts that in Hyman et al. less than half (44%) of the highly amplified genes showed mRNA over expression (see abstract). According to the Examiner, it is not more likely than not that amplified DNA=amplified mRNA=amplified polypeptides. The Examiner

asserts that polypeptide levels were not investigated and therefore do not speak to the relationship between mRNA levels and polypeptide levels, which is the issue here.

According to the Examiner, Pollack et al did not investigate polypeptide levels and therefore does not speak to the issue of the correlation of levels of mRNA and encoded polypeptide. The Examiner asserts that Pollack et al also noted contradictory results found by another research group, noting that, "Alternatively, the contrasting findings for amplified genes may represent real biological differences between breast and metastatic colon tumors: resolution of this issue will require further studies" (page 12,968 end of first paragraph). The Examiner maintains that Pollack et al does not support the asserted utility of the claimed invention.

The Examiner asserts that the Declaration by Dr. Ashkenazi was unpersuasive. According to the Examiner, there is no evidence that clinicians use information about a gene product NOT being overexpressed as a basis for deciding to not treat a patient with an agent that targets that gene product. The Examiner asserts that the role of PRO1411 in cancer is not set forth in the specification and it is not clear how the specification leads a clinical to a "better determination of suitable therapy" as asserted by Applicants.

The Examiner asserts that the article by Hanna et al. is unpersuasive. According to the Examiner, Hanna et al. say that these tests are used more or less independently, with the protein test used first, followed by the gene test if the protein test is negative (column 2, third full paragraph). The Examiner asserts that the protein test is only necessary to determine the appropriateness of antibody therapy. Also, it is stated in the same paragraph that "in general, FISH [gene] and IHC [protein] results correlate well for Her-2. However, subsets of breast tumors are found that demonstrate discordant results, i.e. protein overexpression without gene amplification or lack of protein overexpression with gene amplification. The clinical significance of such results is unclear." Therefore, according to the Examiner, the issues of Her-2 and breast cancer cannot be generalized to any gene expressed in any tumor. As such, the Examiner maintains that Hanna et al. is not dispositive of the central issue herein, the correlation of gene levels, mRNA levels and protein levels and predictability thereof.

According to the Examiner, one skilled in the art would not assume that a small increase in gene copy number would correlate with significantly increased mRNA levels or encoded polypeptide levels. Pennica et al was cited as evidence showing a lack of correlation between

gene (DNA) amplification and elevated mRNA levels. Konopka et al (PNAS, 83:4049-52,1986) was cited as stating that "Protein expression is not related to amplification of the *abl* gene but to variation in the level of bcr-abl mRNA production from a single Ph1 template" (see abstract). According to the Examiner, Konopka et al also provide evidence that showing lack of correlation between gene amplification and increased polypeptide level. Gokman-Polar et al and Lewin were cited as teaching the lack of correlation between mRNA levels and protein levels. Finally, the Examiner asserts that it is noted that the literature of record cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissues. Haynes et al was cited to provide evidence that polypeptides levels cannot be accurately predicted from mRNA levels, and that variances as much as 40-fold or even 50 fold were not uncommon (page 1863). According to the Examiner, given the asserted "visible 2-fold increase in mRNA" (Declaration Dr. Grimaldi previously submitted as Exhibit 1) and the evidence presented by Haynes et al, Gokman-Polar et al and Lewin, it is clear that one skilled in the art would not assume that a small increase/decrease in mRNA would correlate with corresponding changes in polypeptide levels or role in desease. According to the Examiner, given the evidence provided by Haynes, Pennica et al and Konopka et al, one skilled in the art would not assume that a small increase in gene copy number would correlate with significantly increased mRNA levels or encoded polypeptide levels.

Utility – Legal Standard

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic tool without also identifying the condition that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. § 2107.01 cautions, however, that Office personnel must

be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, *any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient,* at least with regard to defining a 'substantial' utility." (M.P.E.P. § 2107.01, emphasis added).

Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P. § 2107 II(B)(1) gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose ... and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Utility need NOT be Proved to a Statistical Certainty – a Reasonable Correlation between the Evidence and the Asserted Utility is Sufficient

An Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). *See, also In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977). Compliance with 35 U.S.C. § 101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the evidence, or "more likely than not" standard. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). This is stated explicitly in the M.P.E.P.:

> [T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." **Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty**. Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not. M.P.E.P. at § 2107.02, part VII (2004) (underline emphasis in original, bold emphasis added, internal citations omitted).

The PTO has the initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Only then does the burden shift to the Applicant to provide rebuttal evidence. *Id.* As stated in the M.P.E.P., such rebuttal evidence does not need to absolutely prove that the asserted utility is real. Rather, the evidence only needs to be reasonably indicative of the asserted utility.

In *Fujikawa v. Wattanasin*, 93 F.3d 1559, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996), the Court of Appeals for the Federal Circuit upheld a PTO decision that *in vitro* testing of a novel pharmaceutical compound was sufficient to establish practical utility, stating the following rule:

> [T]esting is often required to establish practical utility. But the test results **need not absolutely prove** that the compound is pharmacologically active. All that is required is that the tests be "*reasonably* indicative of the desired [pharmacological] response." In other words, there must be **a sufficient correlation** between the tests and an asserted pharmacological activity so as to convince those skilled in the art, **to a reasonable probability**, that the novel compound will exhibit the asserted pharmacological behavior." *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1564, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996) (internal citations omitted, bold emphasis added, italics in original).

While the *Fujikawa* case was in the context of utility for pharmaceutical compounds, the principals stated by the Court are applicable in the instant case where the asserted utility is for a diagnostic use – utility does not have to be established to an absolute certainty, rather, the evidence must convince a person of skill in the art "to a reasonable probability." In addition, the evidence need not be direct, so long as there is a "sufficient correlation" between the tests performed and the asserted utility.

Thus, the legal standard for demonstrating utility is a relatively low hurdle. An Applicant need only provide evidence such that it is **more likely than not that a person of skill in the art would be convinced, to a reasonable probability, that the asserted utility is true**. The evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. The Applicant **does not need to provide evidence such that it establishes an asserted utility as a matter of statistical certainty.**

Even assuming that the PTO has met its initial burden to offer evidence that one of ordinary skill in the art would reasonably doubt the truth of the asserted utility, Applicants assert

that they have met their burden of providing rebuttal evidence such that it is more likely than not those skilled in the art, to a reasonable probability, would believe that the claimed invention is useful as a diagnostic tool for cancer.

Substantial Utility

Summary of Applicants' Arguments and the PTO's Response

In an attempt to clarify Applicants' argument, Applicants offer a summary of their argument and the disputed issues involved. Applicants assert they have provided reliable evidence that mRNA for the PRO1411 polypeptide is more highly expressed in normal skin tissue compared to melanoma, and therefore the claimed nucleic acids are useful as diagnostic tools. Applicants are not asserting that the claimed nucleic acids will necessarily provide a definitive diagnosis of cancer, but rather that they are useful, alone or in combination with other diagnostic tools to assist in the diagnosis of certain cancers. Applicants' asserted utility rests on the following argument:

1. Applicants have provided reliable evidence that mRNA for the PRO1411 polypeptide is more highly expressed in normal skin tissue compared to melanoma;

2. By virtue of their differential expression, the claimed polynucleotides have utility regardless of whether or not the encoded PRO1411 polypeptide is also differentially expressed. However, Applicants assert that it is well-established in the art that a change in the level of mRNA encoding a particular protein, e.g. a decrease, generally leads to a corresponding change in the level of the encoded protein, e.g. a decrease;

3. Given Applicants' evidence that the level of mRNA for the PRO1411 polypeptide is decreased in melanoma compared to normal tissue counterparts, it is likely that the PRO1411 polypeptide is differentially expressed in melanoma.

Applicants understand the PTO to be making several arguments regarding the utility of the claimed polynucleotides:

1. The PTO has challenged the reliability of the evidence reported in Example 18, and states that no data regarding expression levels are provided;

2. The PTO argues that there is no correlation between gene copy number or transcription levels and polypeptide levels;

3. The PTO states that the role of PRO1411 in cancer is unclear.

As detailed below, Applicants submit that the PTO has failed to meet its initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). First, the PTO has failed to offer any evidence to support its rejection of the data in Example 18 and the Declaration of Chris Grimaldi in support of these data. Second, Applicants submit that given the well-established correlation between a change in the level of mRNA with a corresponding change in the levels of the encoded protein, the PRO1411 protein is likely differentially expressed in certain tumors. This provides utility for PRO1411 and related proteins as cancer diagnostic tools. However, utility for the pending claims does not rely on whether the encoded polypeptide is overexpressed, and as such whether or not increased levels of PRO1411 mRNA correlate with increased levels of PRO1411 protein is not presently an issue. Third, whether or not PRO1411 is the causative agent for cancer does not impact its use as a diagnostic tool for certain cancers. Finally, even if the PTO has met its initial burden, Applicants have submitted enough rebuttal evidence to establish that it is **more likely than not** that a person of skill in the art would be convinced, **to a reasonable probability,** that the asserted utility is true. As stated above, **the standard for establishing an asserted utility is not statistical or absolute certainty.**

Applicants have established that the Gene Encoding the PRO1411 Polypeptide is Differentially Expressed in Certain Cancers compared to Normal Tissue

Applicants first address the PTO's argument that the evidence of differential expression of the gene encoding the PRO1411 in melanoma is insufficient. The Examiner maintains that the data presented in Example 18 are preliminary at best, and cannot be evaluated or repeated independently by the skilled artisan. According to the Examiner, the specification does not set forth the number of independent samples tested, the levels of the nucleic acid or protein in the samples such that the "higher" levels in normal tissue as compared to levels in melanoma was determined to be statistically significant. The Examiner asserts that the specification does not set forth the conditions and the probes used to determine the "levels" of SEQ ID NO:51 in the sample tested and the skilled artisan would not know under what conditions and using what probes that a difference in expression could be detected. The Examiner maintains that it is not clear if under/overexpression was detected in 1/10 or 10/10 independent samples tested.

The PTO has stated that the Grimaldi Declaration is insufficient to overcome the rejection of Claims 1-8 and 11-13 . The PTO argues that Example 18 is insufficient because it does not teach what the level of expression is, because it is not clear how many samples would be required, whether a pooled sample is required as the normal tissue and what sensitivity would be needed. The PTO also argues that one cannot determine if the observed "decrease" is due to a mutation, copy number differences or transcription rates.

Applicants maintain that the data in Example 18 are sufficient to establish that the mRNA encoding the PRO1411 polypeptide is more highly expressed in normal skin tissue compared to melanoma. Gene expression was analyzed using standard semi-quantitative PCR amplification reactions of cDNA libraries isolated from different human tumor and normal human tissue samples. Identification of the differential expression of the PRO1411 polypeptide-encoding gene in tumor tissue compared to the corresponding normal tissue renders the molecule useful as a diagnostic tool for the determination of the presence or absence of tumor. In support, Applicants previously submitted as Exhibit 1 a first Declaration of J. Christopher Grimaldi, an expert in the field of cancer biology. This declaration explains the importance of the data in Example 18, and how differential gene and protein expression studies are used to differentiate between normal and tumor tissue (see Declaration, paragraph 7).

In paragraph 5 of his declaration, Mr. Grimaldi states that the gene expression studies reported in Example 18 of the instant application were made from pooled samples of normal and of tumor tissues. Mr. Grimaldi explains that:

> The DNA libraries used in the gene expression studies were made from pooled samples of normal and of tumor tissues. *Data from pooled samples is more likely to be accurate than data obtained from a sample from a single individual.* That is, the detection of variations in gene expression is likely to represent a more generally relevant condition when pooled samples from normal tissues are compared with pooled samples from tumors in the same tissue type. (Paragraph 5) (emphasis added).

Thus, contrary to the PTO's position, the use of pooled samples increases the accuracy of the expirement. With respect to the PTO's concerns about whether a clinician would need to use pooled normal samples in assessing a sample from a patient to determine whether the patient might have melanoma, Applicants note that pooled samples were used in the above experiments

to enhance the accuracy of the initial identification of differentially expressed polypeptides. However, the fact that pooled samples were used in the initial identification of the differentially expressed polypeptides does not impart a requirement that the normal control samples used by a clinician be pooled. In fact, Applicants note that there are many protein based diagnostics on the market in which the level of a particular protein is assessed to determine whether a patient may be suffering from a particular condition. These assays do not necessarily require that a control sample be directly compared to the test sample. Instead, a normal range of protein levels is initially defined and the amount of protein in the patient sample is quantitated to determine whether it is outside of the normal range. Accordingly, the use of the encoded polypeptides as a diagnostic marker requires only the use of standard assay technology. The same is true regarding the number of samples required and the sensitivity necessary. Again, the fact that pooled samples were used in the initial identification does not mean that multiple samples are required to use the encoded polypeptides as diagnostic markers, nor does it suggest that the required sensitivity is any different than that typically required for protein based diagnostics.

With respect to the Examiner's concerns regarding the methodology used to compare mRNA levels in normal tissue to that in cancerous tissue in Example 18, Applicants maintain that this methodology is reliable. In paragraphs 6 and 7, Mr. Grimaldi explains that the semi-quantitative analysis employed to generate the data of Example 18 is sufficient to determine if a gene is over- or under-expressed in tumor cells compared to corresponding normal tissue. He states that any visually detectable difference seen between two samples is indicative of at least a two-fold difference in cDNA between the tumor tissue and the counterpart normal tissue. Thus, the results of Example 18 reflect at least a two-fold difference between normal and tumor samples. Furthermore, Applicants provide herewith as Exhibit 1 a copy of page 122 of the 2002-2003 New England Biolabs catalog. Exhibit 1 shows DNA size markers of differing lengths run on an agarose gel. The column on the left provides the mass of each marker in nanograms and the column on the right provides the length of the marker. It is apparent that the band intensity of markers having mass differences of two fold are readily distinguishable by eye (See for example, the difference in band intensities of the 0.1kb fragment present at 61ng and the 0.5kb marker present at 124ng). Accordingly, Applicants maintain that the procedures used to detect differences in expression levels were sufficiently sensitive to detect two-fold differences.

In addition, Applicants note that Dr. Grimaldi also states that the results of the gene expression studies indicate that the genes of interest "can be used to differentiate tumor from normal," thus establishing their reliability. He explains that, contrary to the PTO's assertions, "The precise levels of gene expression are irrelevant; what matters is that there is a relative difference in expression between normal tissue and tumor tissue." (Paragraph 7). Thus, since it is the relative level of expression between normal tissue and suspected cancerous tissue that is important, the precise level of expression in normal tissue is irrelevant. Likewise, there is no need for quantitative data to compare the level of expression in normal and tumor tissue. As Mr. Grimaldi states, "If a difference is detected, this indicates that the gene and its corresponding polypeptide and antibodies against the polypeptide are useful for diagnostic purposes, to screen samples to differentiate between normal and tumor."

Applicants submit that the declaration of Mr. Grimaldi is based on personal knowledge of the relevant facts at issue. Mr. Grimaldi is an expert in the field and conducted or supervised the experiments at issue. Applicants remind the PTO that "[o]ffice personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned." PTO Utility Examination Guidelines (2001) (emphasis added). In addition, declarations relating to issues of fact should not be summarily dismissed as "opinions" without an adequate explanation of how the declaration fails to rebut the Examiner's position. *In re Alton* 76 F.3d 1168 (Fed. Cir. 1996). The PTO has not supplied any reasons or evidence to question the accuracy of the facts upon which Mr. Grimaldi based his opinion. Mr. Grimaldi has personal knowledge of the relevant facts, has based his opinion on those facts, and the PTO has offered no reason or evidence to reject either the underlying facts or his opinion. Therefore, the PTO should accept Mr. Grimaldi's opinion with regard to his statement that "any visually detectable difference seen between two samples is indicative of at least a two-fold difference in cDNA between the tumor tissue and the counterpart normal tissue" and that the genes of interest "can be used to differentiate tumor from normal." Together, these statements establish that there is at least a two-fold difference in expression, and that the results are reliable enough that they can be used to distinguish tumor from normal tissue. Finally, Applicants submit that whether this differential expression is due to an increase in chromosomal copy number or increased

transcription rates is not relevant to whether the difference in expression can be used to distinguish tumor from normal tissue.

The PTO has recognized that the utility of a nucleic acid does not depend on the function of the encoded gene product. The Utility Examination Guidelines published on January 5, 2001 state "In addition, the utility of a claimed DNA does not necessarily depend on the function of the encoded gene product. A claimed DNA may have a specific and substantial utilty because, e.g. it hybridizes near a disease-associated gene or it has a gene regulating activity." (Federal Register, Volume 66, page 1095, Comment 14). While Applicants appreciate that actions taken in other applications are not binding on the PTO with respect to the present application, Applicants note that the PTO issues patents relating to nucleic acids which are useful for diagnosing particular conditions regardless of whether the nucleic acids are the causative agent for the condition. For example, polymorphisms which are indicative of a predisposition to a particular condition are patentable (*see, e.g.,* U.S. Patent No. 6,465,185, U.S. Patent No. 6,228,582, and U.S. Patent No. 6,162,604 submitted herewith as Exhibits 2-4), even though they may or may not cause the disease itself. Similarly, the present nucleic acids which are useful for determining whether an individual has cancer are useful regardless of whether or not they are the cause of the cancer.

In conclusion, Applicants submit that the evidence reported in Example 18, combined with the first Grimaldi Declaration, establishes that there is at least a two-fold difference in PRO1411 cDNA between normal skin tissue and melanoma. Therefore, it follows that expression levels of the PRO1411 gene can be used to distinguish normal skin tissue from melanoma. The PTO has not offered any significant arguments or evidence to the contrary.

Applicants have established that the Accepted Understanding in the Art is that there is a Direct Correlation between mRNA Levels and the Level of Expression of the Encoded Protein

Because the claims have been amended such that the claimed nucleic acids are not defined by the sequence of the polypeptide they encode, the question of whether there is a correlation between changes in gene expression and changes in protein expression are not presently at issue. However, Applicants submit that they have established for the record that it is well-established in the art that a change in the level of mRNA for a particular protein, generally leads to a corresponding change in the level of the encoded protein. Given Applicants' evidence

of differential expression of the mRNA for the PRO1411 polypeptide in melanoma, it is more likely than not that the PRO1411 polypeptide is also differentially expressed.

The Examiner asserts that mRNA levels and protein levels are not inexorably related, in that an increase in one necessarily leads to an increase in all of them.

The Examiner cites Haynes et al. (1998, Electrophoresis 19:1862-1871), as showing that the protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript. Applicants submit that Haynes does not contradict the utility or enablement of the instant claims. Haynes is a review article dealing with the art of proteome analysis. The assertions in Haynes cited by the Examiner were made in an effort to identify shortcomings in the art of mRNA quantification to argue for "proteome analysis to become an essential component in the comprehensive analysis of biological systems." Haynes, p. 1863. Haynes studied 80 selected samples from *Saccharomyces cerevisiae*, and reported "a general trend but no strong correlation between protein and transcript levels (Fig. 1)." Id. However, a cursory inspection of Fig. 1 shows a clear correlation between the mRNA levels and protein levels measured. This correlation is confirmed by an inspection of the full-length research paper from which the data in Fig. 1 were derived, presented herein as Exhibit 5 (Gygi et al., Molecular and Cellular Biology, Mar. 1999, 1720-1730). Gygi states that "there was a general trend of increased protein levels resulting from increased mRNA levels," with a correlation coefficient of 0.935, indicating a strong correlation. Gygi, p. 1726. Moreover, Gygi also states that the correlation is especially strong for highly expressed mRNAs. Id. Considering that Example 18 of the specification shows higher expression of PRO1411 mRNA in normal skin tissue compared to melanoma, Haynes and Gygi actually provide strong evidence in support of a general correlation between mRNA and protein levels.

The 50-fold variation referred to by Haynes and cited by the Examiner, does not in any way show the absence of a correlation between mRNA and protein levels, but rather identifies the outer limits of variability in the authors' experiments. This variability may support the authors' assertion that the amount of a particular protein cannot accurately predict the particular level of the corresponding mRNA transcript, but it does not suggest an absence of a general correlation between mRNA and protein levels. Again, Applicants' utility is based on the differential expression of mRNA in normal skin tissue versus melanoma. Exact levels of

expression are irrelevant. Moreover, Gygi states that the high degree of variability seen at low levels of mRNA (shown in inset of Fig. 1, Haynes p. 1863) is due to the fact that "the magnitude of the error in the measurement of mRNA levels is inversely proportional to the mRNA levels." Gygi, p. 1727. Considering that PRO1411 mRNA has been shown in Example 18 of the specification to be more highly expressed in normal skin tissue than melanoma, the variability identified by Haynes is even less applicable to establishing the absence of a correlation between mRNA and protein levels in the instant case.

As stated above, the standard for utility is not absolute certainty, but rather whether one of skill in the art would be more likely than not to believe the asserted utility. As discussed above, Applicants maintain that by virtue of their differential expression the claimed polynucleotides possess utility regardless of whether or not the PRO1411 polypeptide is differentially expressed. However, Applicants maintain that it is more likely than not that the PRO1411 polypeptide is differentially expressed. Applicants note that the utility requirement does not require Applicants to show that mRNA levels correlate to protein levels in every case. The data presented in Haynes is not inconsistent with or contradictory to the utility or enablement of the instant claims. To the contrary, the data clearly show a general correlation between protein levels and mRNA levels, and thus support Applicants' assertion that such a general correlation exists.

Even if Haynes supported the Examiner's argument, which it does not, one contrary example does not establish that one of skill in the art would find it is more likely than not there is no general correlation between mRNA level and protein levels. In fact, the working hypothesis among those skilled in the art, as illustrated by the evidence presented herein by Applicants, is that there is a direct correlation between mRNA levels and protein levels. This is further supported by the statement in Haynes that "interpretations of quantitative mRNA expression profiles frequently implicitly or explicitly assume that for specific genes the transcript levels are indicative of the levels of protein expression." See, Haynes, p. 1863, first full paragraph. Haynes does not suggest there is no correlation between mRNA and protein levels, but rather points to what the authors believe are shortcomings of using mRNA quantification to predict protein levels; specifically, that mRNA levels may not accurately predict protein levels *in each particular instance*. Considering the more likely than not standard for utility, Haynes'

identification of reasons why proteomic analysis may be preferable in some cases does not contradict Applicants' evidence that there is a general correlation between mRNA and protein levels.

The Examiner also cites the textbook by Lewin as teaching that "... production of RNA cannot be inevitably be equated with production of protein" (page 487, column 2, last paragraph). Applicants note that Lewin's textbook, Genes VI, (Benjamin Lewin, Genes VI (1997)) (submitted herewith as Exhibit 6) states "having acknowledged that control of gene expression can occur at multiple stages, and that production of RNA cannot inevitably be equated with production of protein, it is clear that the overwhelming majority of regulatory events occur at the initiation of transcription." *Genes VI* at 847-848 (emphasis added).

According to the Examiner, the lack of correlation between mRNA and protein levels is is reconfirmed by a variety of studies such as that evidenced by Gokman-Polar et al (Cancer Research 61:1375-1381, 2001) that indicates the absence of any necessary correlation between increased mRNA levels and increased protein levels. With respect to the Gokman-Polar reference cited by the Examiner, the PTO relies on a statement from Gokman-Polar that "Quantitative reverse transcription-PCR analysis revealed that the PKC mRNA levels do not directly correlate with PKC protein levels, indicating that PKC isoenzyme expression is likely regulated at the posttranscriptional/translational level." Office Action at 8. However, a close review of the entire article indicates that with one exception, the trend in the data is that mRNA and protein levels are positively correlated, supporting Applicants assertion that increased mRNA levels correlate with increased protein levels. In Figure 2, the protein level of two isozymes shows a decrease, while the third is increased. This same pattern is seen for the corresponding mRNA levels in Figure 6, although admittedly the increase in mRNA for the third isozyme is minimal. Similarly, comparing the protein levels of the three isozymes in Figure 4 to the corresponding mRNA levels in Figure 7, with one exception the mRNA levels are positively correlated to protein levels. While protein levels do not increase or decrease in direct proportion to the changes in mRNA, the trend in five of the six examples is that protein levels are positively correlated to mRNA levels. This evidence is hardly sufficient to establish that one of skill in the art would reasonably doubt that there is a reasonable correlation between mRNA levels and protein levels.

The Examiner cites Pennica et al (PNAS, 95:14717-22, 1998) as showing that there is a lack of correlation between gene amplification and protein expression of the WISP protein and asserts that this teaching in combination with Haynes et al indicates that there is no significant correlation between nucleic acid level and translation. Applicants have addressed Haynes et al. above. With respect to Pennica et al. Applicants note that Pennica relates to gene amplification (i.e. increased copy number). In contrast, the data in Example 18 was obtained by performing quantitative PCR on cDNA libraries. Thus, the data in Example 18 reflects mRNA levels rather than copy number. Furthermore, Pennica does not look at protein levels and does not address the relationship between mRNA levels and polypeptide levels.

Hu et al. (2003, Journal of Proteome Research 2:405-412) is cited as showing that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. The Examiner acknowledges that Hu shows that, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section). In Hu, the researchers used an automated literature-mining tool to summarize and estimate the relative strengths of all human gene-disease relationships published on Medline. They then generated a microarray expression dataset comparing breast cancer and normal breast tissue. Using their data-mining tool, they looked for a correlation between the strength of the literature association between the gene and breast cancer, and the magnitude of the difference in expression level. They report that for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a *known* role in the disease. *See* Hu at 411. However, among genes with a 10-fold or more change in expression level, there was a strong correlation between expression level and a *published* role in the disease. *Id.* at 412. Importantly, Hu reports that the observed correlation was only found among estrogen receptor-positive tumors, not ER-negative tumors. *Id.*

The general findings of Hu are not surprising – one would expect that genes that have the greatest change in expression in a disease would be the first targets of research, and therefore have the strongest *known* relationship to the disease as measured by the number of reports of a connection in the literature. But this does not mean that genes, and their corresponding proteins,

with a lower level of change in expression are not important or cannot be used as molecular markers of the disease. This is demonstrated by the fact that ER-negative tumors did not show a correlation. The correlation reported in Hu only indicates that the greater the change in expression level, the more likely it is that there is a *published* or *known* role for the gene in the disease, as found by their automated literature-mining software. Nowhere in Hu does it say that a lack of correlation in their study means that the genes, and their corresponding proteins, with a less than five-fold change in level of expression in cancer cannot serve as a molecular marker of cancer. Genes with lower levels of change in expression may or may not be the most important genes in causing the disease, but the genes and their corresponding proteins can still show a consistent and measurable change in expression. While such genes and polypeptides may or may not be good targets for further research, they can nonetheless be used as diagnostic tools. Thus, Hu does not refute the Applicants' assertion that the PRO1411 polypeptide, can be used as a cancer diagnostic tool because it is differentially expressed in certain tumors.

As discussed above, Applicants maintain that the claimed polynucleotides possess utility regardless of whether or not the encoded polypeptides are differentially expressed. However, Applicants assert that it is more likely than not that a polypeptide encoded by a differentially expressed mRNA is differentially expressed. Applicants previously submitted a copy of a second Declaration by J. Christopher Grimaldi, an expert in the field of cancer biology (previously attached as Exhibit 2). As stated in paragraph 5 of the declaration, "Those who work in this field are well aware that in the vast majority of cases, when a gene is over-expressed...the gene product or polypeptide will also be over-expressed.... This same principal applies to gene under-expression." Further, "the detection of increased mRNA expression is expected to result in increased polypeptide expression, and the detection of decreased mRNA expression is expected to result in decreased polypeptide expression. The detection of increased or decreased polypeptide expression can be used for cancer diagnosis and treatment." The references cited in the declaration and submitted herewith support this statement.

The Examiner states that the second Declaration of Dr. Grimaldi is unpersuasive because the therapeutic antibodies in the art rely upon statistically relevant increased polypeptide expression or unique polypeptide expression. According to the Examiner, there is no basis for asserting that therapeutic antibodies would be useful in a scenario where the protein is under-

expressed in the tumor. Applicants maintain that antibodies against the encoded polypeptides can be used for diagnostic purposes.

The Examiner also asserts that the second Declaration of Dr. Grimaldi is not persuasive because the statement that increased mRNA expression is expected to be associated with increased protein production is Declarant's opinion and is not supported by fact or evidence. As discussed above, Applicants submit that the declaration of Mr. Grimaldi is based on personal knowledge of the relevant facts at issue. Mr. Grimaldi is an expert in the field and conducted or supervised the experiments at issue. Applicants remind the PTO that "[o]ffice personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned." PTO Utility Examination Guidelines (2001) (emphasis added). In addition, declarations relating to issues of fact should not be summarily dismissed as "opinions" without an adequate explanation of how the declaration fails to rebut the Examiner's position. *In re Alton* 76 F.3d 1168 (Fed. Cir. 1996). The PTO has not supplied any reasons or evidence to question the accuracy of the facts upon which Mr. Grimaldi based his opinion. Mr. Grimaldi has personal knowledge of the relevant facts, has based his opinion on those facts, and, as discussed herein, the PTO has not offered sufficient evidence to reject either the underlying facts or his opinion. Therefore, the PTO should accept Mr. Grimaldi's opinion with regard to his statement that "in the vast majority of cases, when a gene is over-expressed...the gene product or polypeptide will also be over-expressed.... This same principal applies to gene under-expression."

Applicants also previously submitted a copy of the declaration of Paul Polakis, Ph.D. (previously attached as Exhibit 3), an expert in the field of cancer biology. As stated in paragraph 6 of his declaration:

> Based on my own experience accumulated in more than 20 years of research, including the data discussed in paragraphs 4 and 5 above [showing a positive correlation between mRNA levels and encoded protein levels in the vast majority of cases] and my knowledge of the relevant scientific literature, it is my considered scientific opinion that for human genes, an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell. In fact, *it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein.* (Emphasis added).

Dr. Polakis acknowledges that there are published cases where such a correlation does not exist, but states that it is his opinion, based on over 20 years of scientific research, that "such reports are exceptions to the commonly understood general rule that increased mRNA levels are predictive of corresponding increased levels of the encoded protein." (Polakis Declaration, paragraph 6).

The Examiner asserts that the Declaration of Dr. Polakis is unpersuasive because it does not provide data such that the Examiner can independently draw conlusions or provide any objective evidence. As discussed above, Applicants submit that the declaration of Dr. Polakis is based on personal knowledge of the relevant facts at issue. Dr. Polakis is an expert in the field. Applicants remind the PTO that "[o]ffice personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned." PTO Utility Examination Guidelines (2001) (emphasis added). In addition, declarations relating to issues of fact should not be summarily dismissed as "opinions" without an adequate explanation of how the declaration fails to rebut the Examiner's position. *In re Alton* 76 F.3d 1168 (Fed. Cir. 1996). The PTO has not supplied any reasons or evidence to question the accuracy of the facts upon which Dr. Polakis based his opinion. Dr. Polakis has personal knowledge of the relevant facts, has based his opinion on those facts, and, as discussed herein, the PTO has not offered sufficient evidence to reject either the underlying facts or his opinion. Therefore, the PTO should accept Dr. Polakis' statement that "it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein."

The Examiner also asserts that, unlike Her2/Neu, PRO1411 has not been associated with tumor formation or the development of cancer, nor has it been shown to be predictive of such. Applicants submit that a lack of known role for PRO1411 in cancer does not prevent its use as a diagnostic tool for cancer. In fact the Revised Interim Utility Guidelines promulgated by the PTO recognize that proteins which are differentially expressed in cancer have utility. (*See* the caveat in Example 12 which state that the utility requirement is satisfied where a protein is expressed in melanoma cells but not on normal skin and antibodies against the protein can be used to diagnose cancer.) In addition, while Applicants appreciate that actions taken in other applications are not binding on the PTO with respect to the present application, Applicants note

that the PTO has issued several patents claiming differentially expressed polypeptides. (*See, e.g.*, U.S. Patent No. 6,414,117 and U.S. Patent No. 6,124,433, attached hereto as Exhibits 7 and 8.)

Contrary to the position of the PTO, the correlation between mRNA levels and protein levels is supported by the art. The statements of Grimaldi and Polakis are supported by the teachings in Molecular Biology of the Cell, a leading textbook in the field (Bruce Alberts, *et al.*, Molecular Biology of the Cell (3rd ed. 1994) (submitted herewith as Exhibit 9) and (4th ed. 2002) (submitted herewith as Exhibit 10)). Figure 9-2 of Exhibit 9 shows the steps at which eukaryotic gene expression can be controlled. The first step depicted is transcriptional control. Exhibit 9 provides that "[f]or most genes transcriptional controls are paramount. This makes sense because, of all the possible control points illustrated in Figure 9-2, only transcriptional control ensures that no superfluous intermediates are synthesized." Exhibit 9 at 403 (emphasis added). In addition, the text states that "Although controls on the initiation of gene transcription are the predominant form of regulation for most genes, other controls can act later in the pathway from RNA to protein to modulate the amount of gene product that is made." Exhibit 9 at 453 (emphasis added). Thus, as established in Exhibit 9, the predominant mechanism for regulating the amount of protein produced is by regulating transcription initiation.

In Exhibit 10, Figure 6-3 on page 302 illustrates the basic principle that there is a correlation between increased gene expression and increased protein expression. The accompanying text states that "a cell can change (or regulate) the expression of each of its genes according to the needs of the moment – *most obviously by controlling the production of its mRNA*." Exhibit 10 at 302 (emphasis added). Similarly, Figure 6-90 on page 364 of Exhibit 10 illustrates the path from gene to protein. The accompanying text states that while potentially each step can be regulated by the cell, "the initiation of transcription is the most common point for a cell to regulate the expression of each of its genes." Exhibit 10 at 364 (emphasis added). This point is repeated on page 379, where the authors state that of all the possible points for regulating protein expression, "[f]or most genes transcriptional controls are paramount." Exhibit 10 at 379 (emphasis added).

Additional support is also found in Zhigang *et al.*, World Journal of Surgical Oncology 2:13, 2004, submitted herewith as Exhibit 11. Zhigang studied the expression of prostate stem cell antigen (PSCA) protein and mRNA to validate it as a potential molecular target for diagnosis

and treatment of human prostate cancer. The data showed "a high degree of correlation between PSCA protein and mRNA expression" Exhibit 11 at 6. Of the samples tested, 81 out of 87 showed a high degree of correlation between mRNA expression and protein expression. The authors conclude that "it is demonstrated that PSCA protein and mRNA overexpressed in human prostate cancer, and that the increased protein level of PSCA was resulted from the upregulated transcription of its mRNA." Exhibit 11 at 11. Even though the correlation between mRNA expression and protein expression occurred in 93% of the samples tested, not 100%, the authors state that "PSCA may be a promising molecular marker for the clinical prognosis of human Pca and a valuable target for diagnosis and therapy of this tumor." *Id.*

Further, Meric *et al.*, Molecular Cancer Therapeutics, vol. 1, 971-979 (2002), submitted herewith as Exhibit 12, states the following:

> The **fundamental principle** of molecular therapeutics in cancer is to exploit the differences in gene expression between cancer cells and normal cells...[M]ost efforts have concentrated on identifying differences in gene expression at the level of mRNA, which can be attributable to either DNA amplification or to differences in transcription. Meric *et al.* at 971 (emphasis added).

Those of skill in the art would not be focusing on differences in gene expression between cancer cells and normal cells if there were no correlation between gene expression and protein expression.

Together, the declarations of Grimaldi and Polakis, the accompanying references, and the excerpts and references provided above all establish that the accepted understanding in the art is that there is a reasonable correlation between changes in gene expression and the level of the encoded protein.

The Examiner asserts that the Orntoft et al., Hyman et al., and Pollack et al. references submitted by the Applicants were unpersuasive. The Examiner maintains that Orntoft et al did not look at gene amplification, mRNA levels and polypeptide levels from a single gene at a time. According to the Examiner, Orntoft et al concentrated on regions of chromosome with strong gains of chromosomal material containing clusters of genes (page 40). The Examiner asserts that this analysis was not done for PRO1411. According to the Examiner, it is not clear whether or not PRO1411 is in a gene cluster in a region of the chromosome that is highly amplified. The

Examiner asserts that in Hyman et al less than half (44%) of the highly amplified genes showed mRNA over expression (see abstract). According to the Examiner, polypeptide levels were not investigated and therefore do not speak to the relationship between mRNA levels and polypeptide levels, which is the issue here.

According to the Examiner, Pollack et al did not investigate polypeptide levels and therefore does not speak to the issue of the correlation of levels of mRNA and encoded polypeptide. The Examiner asserts that Pollack et al also noted contradictory results found by another research group, noting that, "Alternatively, the contrasting findings for amplified genes may represent real biological differences between breast and metastatic colon tumors: resolution of this issue will require further studies" (page 12,968 end of first paragraph). The Examiner maintains that Pollack et al does not support the asserted utility of the claimed invention.

Applicants note that, as discussed above, the data in Example 18 reflect mRNA levels, not gene copy number and that, as discussed above, the claimed polynucleotides are useful as diagnostics or therapeutics regardless of whether or not gene amplification plays any role in the overexpression of the polynucleotides. In addition, Applicants note that Orntoft did look at mRNA and protein levels for individual genes located within amplified or deleted chromosomal regions and found that of the 40 proteins analyzed only one showed disagreement between transcript alteration and protein alteration (Orntoft, page 42). Hyman looked at the correlation between gene copy number and mRNA levels and did not look at polypeptide levels. However, Hyman observed that "the results illustrate a considerable influence of copy number on gene expression patterns." The Pollack reference also examined the mRNA levels of individual genes within amplified regions, although polypeptide levels were not examined. Pollack concluded "that on average a 2-fold change in copy number is associated with a corresponding 1.5-fold change in mRNA levels." (Pollack, abstract)

The Examiner asserts that the Declaration by Dr. Ashkenazi was unpersuasive. According to the Examiner, there is no evidence that clinicians use information about a gene product NOT being overexpressed as a basis for deciding to not treat a patient with an agent that targets that gene product. Dr. Ashkenazi's Declaration points out that there are situations where it is useful to quantitate both nucleic acid levels and protein levels. In particular, Dr. Ashkenazi points out that in situations where over-expression of the gene product does not parallel gene

amplification in certain tumor types but does so in others, then parallel monitoring of gene amplification and gene product over-expression enables more accurate tumor classification and hence better determination of suitable therapy. In such situations, absence of over-expression is crucial information for the practicing clinician. If a gene is amplified but the corresponding gene product is not over-expressed, the clinician accordingly will decide not to treat a patient with agents that target that gene product. Applicants continue to maintain, however, that in most instances differential expression of a nucleic acid results in differential expression of the encoded polypeptide.

The Examiner asserts that the article by Hanna et al. is unpersuasive. According to the Examiner, Hanna et al. say that these tests are used more or less independently, with the protein test used first, followed by the gene test if the protein test is negative (column 2, third full paragraph). The Examiner asserts that the protein test is only necessary to determine the appropriateness of antibody therapy. Also, it is stated in the same paragraph that "in general, FISH [gene] and IHC [protein] results correlate well for Her-2. However, subsets of breast tumors are found that demonstrate discordant results, i.e. protein overexpression without gene amplification or lack of protein overexpression with gene amplification. The clinical significance of such results is unclear." Therefore, according to the Examiner, the issues of Her-2 and breast cancer cannot be generalized to any gene expressed in any tumor. As such, the Examiner maintains that Hanna et al. is not dispositive of the central issue herein, the correlation of gene levels, mRNA levels and protein levels and predictability thereof.

The Hanna article teaches that the HER-2/neu gene has been shown to be amplified and/or over-expressed in 10%-30% of invasive breast cancers and in 40-60% of intraductal breast carcinoma. Further, the article teaches that diagnosis of breast cancer includes testing both the amplification of the HER-2/neu gene (by FISH) as well as the over-expression of the HER-2/neu gene product (by IHC). Even when the protein is not over-expressed, the assay relying on both tests leads to a more accurate classification of the cancer and a more effective treatment of it. Thus, as pointed out in the Declaration of Dr. Ashkenazi, quantitation of the polypeptide levels assists a physician in selecting an appropriate therapy in those instances where the polypeptide is differentially expressed in certain tumor types but not in others.

The Examiner cites Pennica et al., Konopka et al., Gokman-Polar et al. and Haynes et al. as indicating that one skilled in the art would not assume that small increases in gene copy number correlate with significantly increased mRNA levels or encoded polypeptide levels. Applicants have addressed Pennica et al., Gokman-Polar et al. and Haynes et al. above. With respect to Konopka et al., the PTO cites Konopka in further support of the assertion that it is not the norm that levels of mRNA correlate with corresponding protein levels. The PTO has confused the relationship between an increase in copy number of a gene and the level of mRNA on the one hand, with the relationship between mRNA expression and levels of the corresponding protein on the other. In particular, the PTO cites the statement in Konopka that "protein expression is not related to amplification of the abl gene but to variation in the level of the bcr-abl mRNA produced from a single Ph1 template." The results presented in Konopka actually present strong evidence in support of Applicants' position that there is a general understanding in the art that levels of mRNA correlate with levels of the corresponding proteins. Konopka analyzed the expression patterns of a gene associated with certain cancers. The authors show a wide variation in the levels of the protein in various cell types, and find that this variation can be attributed to the levels of the corresponding mRNA in each cell type. See, Konopka, p. 4050. Konopka thus concludes, "these combined data suggest that differential bcr-abl mRNA expression from a single gene template is responsible for the variable levels of $P210^{c\text{-}abl}$ [the protein of interest] detected." Id., p. 4051. Thus, far from supporting the PTO's assertion that it is not the norm that increased transcription leads to increased levels of the corresponding protein, Konopka strongly supports the opposite proposition asserted by Applicants - that the level of mRNA, more often than not, correlates with the level of the corresponding protein.

The Arguments made by the PTO are Not Sufficient to satisfy the PTO's Initial Burden of Offering Evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility"

As stated above, an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the

evidence, or "more likely than not" standard. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). This is stated explicitly in the M.P.E.P.:

> [T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." **Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty**. Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not. M.P.E.P. at § 2107.02, part VII (2004) (underline emphasis in original, bold emphasis added, internal citations omitted).

The PTO has the initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Only then does the burden shift to the Applicant to provide rebuttal evidence. *Id.* As stated in the M.P.E.P., such rebuttal evidence does not need to absolutely prove that the asserted utility is real. Rather, the evidence only needs to be reasonably indicative of the asserted utility.

The PTO has not offered any arguments or cited any references to establish "that one of ordinary skill in the art would reasonably doubt" that a gene differentially expressed in certain tumors can be used as a diagnostic tool. Given the lack of support for the PTO's position, Applicants submit that the PTO has not met its initial burden of overcoming the presumption that the asserted utility is sufficient to satisfy the utility requirement. And even if the PTO has met that burden, the Applicants' supporting rebuttal evidence is sufficient to establish that one of skill in the art would be more likely than not to believe that the claimed nucleic acids can be used as diagnostic tools for cancer, particularly melanoma.

Specific Utility

The Asserted Substantial Utilities are Specific to the Claimed Nucleic Acids

Applicants have provided a specific utility for the claimed nucleic acids. Specific Utility is defined as utility which is "specific to the subject matter claimed," in contrast to "a general utility that would be applicable to the broad class of the invention." M.P.E.P. § 2107.01 I. Applicants submit that the evidence of differential expression of the PRO1411 gene in certain types of tumor cells, along with the declarations and references discussed above, provide a specific utility for the claimed nucleic acids.

As discussed above, there are significant data which show that the PRO1411 gene is more highly expressed in normal skin tissue compared to melanoma. These data are strong evidence that the PRO1411 gene is associated with melanoma. Thus, contrary to the assertions of the PTO, Applicants submit that they have provided evidence associating the PRO1411 gene with a specific disease. The asserted utility as a diagnostic tool for cancer, particularly melanoma, is a specific utility – it is not a general utility that would apply to the broad class of nucleic acids.

Conclusion

The PTO has asserted three arguments to support its conclusion that the differential expression of PRO1411 is not sufficient to establish utility for the claimed polynucleotides:

1. The PTO has challenged the reliability of the evidence reported in Example 18, and states that no data regarding expression levels are provided;

2. The PTO argues that there is no correlation between gene copy number or transcription levels and polypeptide levels;

3. The PTO states that the role of PRO1411 in cancer is unclear.

Applicants have addressed each of these arguments in turn.

First, the Applicants provided a first Declaration of Chris Grimaldi stating that the data in Example 18 are real and significant. This declaration also indicates that given the relative difference in expression levels, the disclosed nucleic acids and corresponding polypeptides have utility as cancer diagnostic tools. The PTO has not offered any substantial reason or evidence to question the data in Example 18, or the first Grimaldi Declaration.

Second, although Applicants maintain that the claimed differentially expressed polynucleotides are useful regardless of whether or not the encoded proteins are differentially expressed, Applicants have shown that the second Grimaldi Declaration and Polakis Declaration, the accompanying references, as well as the excerpts and references cited above, demonstrate that it is well-established in the art that a change in mRNA levels generally correlates to a corresponding change in the encoded protein levels. The PTO has not offered any substantial reason or evidence to question these declarations and supporting references. One of skill in the art will recognize that polypeptides differentially expressed in certain cancers have utility as diagnostic tools for cancer.

Third, Applicants have demonstrated that it is not necessary to know the cause or consequence of the differential expression of PRO1411 nucleic acids and polypeptides in certain tumors in order to use them as diagnostic tools for cancer.

Applicants have pointed out that the substantial utilities described above are specific to the claimed polynucleotides because the PRO1411 gene is differentially expressed in certain cancer cells compared to the corresponding normal cells. This is not a general utility that would apply to the broad class of polynucleotides.

Given the totality of the evidence provided, Applicants submit that they have established a substantial, specific, and credible utility for the claimed polynucleotides as diagnostic tools. According to the PTO Utility Examination Guidelines (2001), irrefutable proof of a claimed utility is not required. Rather, a specific, substantial, and credible utility requires only a "reasonable" confirmation of a real world context of use. Applicants remind the PTO that:

> A small degree of utility is sufficient . . . The claimed invention must only be capable of performing some beneficial function . . . An invention does not lack utility merely because the particular embodiment disclosed in the patent lacks perfection or performs crudely . . . A commercially successful product is not required . . . Nor is it essential that the invention accomplish all its intended functions . . . or operate under all conditions . . . partial success being sufficient to demonstrate patentable utility . . . In short, **the defense of non-utility cannot be sustained without proof of total incapacity**. If an invention is only partially successful in achieving a useful result, a rejection of the claimed invention as a whole based on a lack of utility is not appropriate. M.P.E.P. at 2107.01 (underline emphasis in original, bold emphasis added, citations omitted).

Applicants submit that they have established that it is more likely than not that one of skill in the art would reasonably accept the utility for the claimed polynucleotides set forth in the specification. In view of the above, Applicants respectfully request that the PTO reconsider and withdraw the utility rejection under 35 U.S.C. §101.

Rejection Under 35 U.S.C. §112-Enablement

Claims 1-8, 11-14 and 16-20 were rejected under 35 U.S.C. 112, first paragraph on the assertion that, since the claimed invention is not supported by either a specific, substantial and credible asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention.

As discussed above, Applicants maintain that the claimed polynucleotides possess utility. Accordingly, Applicants respectfully request that this rejection be withdrawn.

Rejection Under 35 U.S.C. §112-Written Description

Claims 1, 2,3,4, 5, 14 and 16-20 were rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The Examiner asserts that the limitation that the isolated nucleic acid is more highly expressed in normal skin cells to relative to melanoma or that the isolated nucleic acid encodes a polypeptide that is more highly expressed in normal skin tissue relative to melanoma does not impart specific structural requirements for possession of nucleic acids. The Examiner asserts that the specification does not teach that the polypeptide *per se* is more highly expressed. According to the Examiner, the specification does not teach variants of either the nucleic acid or polypeptide that have these properties as claimed.

With respect to claims relating to hybridizing nucleic acids, the Examiner asserts that the hybridization is not to SEQ ID NO:51 but encoding variants thereof, which can be up to 30% different than SEQ ID NO:51. The Examiner asserts that the specification fails to provide written description of a single nucleic acid that was isolated by hybridization to either SEQ ID NO:51 or variants of the nucleic acid encoding the polypeptide of SEQ ID NO:52. The Examiner asserts that the actual structure or other relevant identifying characteristics of each nucleic acid that encodes a variant protein having the claimed properties of the underexpressed protein can only be determined empirically by actually making every nucleic acid that encodes the recited variability (i.e. the substitutions, insertions or deletions as compared to SEQ ID NO:51) and testing each to determine whether it encodes a protein having the particularly disclosed properties of the protein of SEQ ID NO:52. The Examiner asserts that the protein disclosed as SEQ ID NO:52, has no disclosed or described biological activity.

The Legal Standard for Written Description

The well-established test for sufficiency of support under the written description requirement of 35 U.S.C. §112 , first paragraph is whether the disclosure "reasonably conveys to artisan that the inventor had possession at that time of the later claimed subject matter." *In re Kaslow*, 707 F.2d 1366, 1375, 2121 USPQ 1089, 1096 (Fed. Cir. 1983); *see also Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at1563, 19 USPQ2d at 1116 (Fed. Cir. 1991). The adequacy of written description support is a factual issue and is to be determined on a case-by-case basis. *See e.g.,*

Vas-Cath, Inc. v. Mahurkar, 935 F.2d at 1563, 19 USPQ2d at 1116 (Fed. Cir. 1991). The factual determination in a written description analysis depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure. *Union Oil v. Atlantic Richfield Co.*, 208 F.3d 989, 996 (Fed. Cir. 2000).

The Current Invention is Adequately Described

As noted above, whether the Applicants were in possession of the invention as of the effective filing date of an application is a factual determination, reached by the consideration of a number of factors, including the level of knowledge and skill in the art, and the teaching provided by the specification. The inventor is not required to describe every single detail of his/her invention. An Applicant's disclosure obligation varies according to the art to which the invention pertains. The present invention pertains to the field of recombinant DNA/protein technology. It is well-established that the level of skill in this field is very high since a representative person of skill is generally a Ph.D. scientist with several years of experience. Accordingly, the teaching imparted in the specification must be evaluated through the eyes of a highly skilled artisan as of the date the invention was made.

The subject matter of the pending claims concerns nucleic acids having 95% or 99% sequence identity to the nucleic acid sequence of SEQ ID NO:51, the full-length coding sequence of the nucleic acid sequence of SEQ ID NO:51, or the full-length coding sequence of the cDNA deposited under ATCC accession number 203245, with the functional recitation as amended: "wherein said isolated nucleic acid is more highly expressed in normal skin tissue compared to melanoma" or "wherein said isolated nucleic acid hybridizes to the complement of a nucleic acid of SEQ ID NO: 51" under the specified conditions. Other claimed nucleic acids are those which hybridize to the nucleic acid sequence of SEQ ID NO:51, the full-length coding sequence of the nucleic acid sequence of SEQ ID NO:51, the full-length coding sequence of the cDNA deposited under ATCC accession number 203245, or the complements thereof, under the specified stringent conditions. We turn first to the claims which recite specific high stringency hybridization conditions.

In *Enzo Biochem v. Gen-Probe Inc.*, 323 F.3d 956 (Fed. Cir. 2002), the Court held that functional descriptions of genetic material may satisfy the written description requirement. In so

holding, the Court gave judicial notice to the USPTO's Manual of Patent Examining Procedure, which provides that the written description requirement may be satisfied when the disclosure provides sufficiently detailed identifying characteristics, such as "complete or partial structure, other physical and/or chemical properties, *functional characteristics when coupled with a known or disclosed correlation between function and structure*, or some combination of such characteristics." *Id.* at 964, quoting 66 Fed. Reg. at 1106 (emphasis in original). In *Enzo*, the Court found describing nucleic acids based on their ability to hybridize to another nucleic acid sequence which was adequately described may be an adequate description of the nucleic acid. This is because the hybridization function of a nucleic acid is dependent on the sequences of the nucleic acid – a disclosed function which is coupled with a known correlation between function and structure. The Court favorably discussed the PTO's example wherein "genus claims to nucleic acids based on their hybridization properties...may be adequately described if they hybridize under highly stringent conditions to known sequences because such conditions dictate that all species within the genus will be structurally similar." *Id.* at 967 (citing *Application of [Written Description] Guidelines*, Example 9) (emphasis added).

Applicants submit that the stringent hybridization conditions specified in the pending claims, alone or in combination with the recited percent sequence identity, result in all species within the genus being structurally similar. As the *Enzo* Court noted, Examples 9 and 10 of the Application of Written Description Guidelines (hereinafter "Guidelines") make clear that specifying hybridization under highly stringent conditions yields "structurally similar DNAs." Guidelines, Example 9 at page 36. The analysis of a genus claim in Example 10 of the Guidelines states:

> [T]urning to the genus analysis, the art indicates that *there is no substantial variation within the [claimed] genus because of the stringency of hybridization conditions which yields structurally similar molecules.* The single disclosed species is representative of the genus because reduction to practice of this species, considered along with the defined hybridization conditions and the level of skill and knowledge in the art, are sufficient to allow the skilled artisan to recognize that applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus. Guidelines, Example 10 at page 39 (emphasis added).

Given the level of skill in the art, specifying highly stringent conditions leads to "no substantial variation within the [claimed] genus," and therefore a skilled artisan would recognize that the Applicants were in possession of the necessary common attributes or features of the genus. This is contrary to the PTO's argument the claimed sequences do not possess "any particular conserved structure, or other disclosed distinguishing feature." (August 3, 2004 Office Action at 7). The common element or attribute of the claimed genus is that species of the genus are structurally related to SEQ ID NO: 51, such that they hybridize to SEQ ID NO: 51 or the related sequences under the specified high stringency conditions recited in the claims.

The present situation is not analogous to *Fiddes v. Baird*, 30 U.S.P.Q. 2d 1481, cited by the PTO. Unlike *Fiddes*, where arguably the structure of other mammalian sequences could not be conceived based on a single species of the genus, here the skill in the art is such that the sequence of nucleic acids which hybridize to SEQ ID NO: 51 under the conditions specified can be conceived. Here, the claimed genus is defined by its structure – members of the genus hybridize under the specified conditions to the specified sequences, each of which are adequately described in the specification.

Applicants submit that the pending claims relating to nucleic acids having 95% or 99% sequence identity to the nucleic acids related to SEQ ID NO:51 with the functional recitation "wherein said isolated nucleic acid is more highly expressed in normal skin tissue compared to melanoma" are also adequately described. In Example 14 of the written description training materials, the written description requirement was found to be satisfied for claims relating to polypeptides having 95% homology to a particular sequence and possessing a particular catalytic activity, even though the applicant had not made any variants. Similarly, the pending claims also have very high sequence homology to the disclosed sequences and must share the same expression pattern in certain tumors. In Example 14, the procedures for making variants were known in the art and the disclosure taught how to test for the claimed catalytic activity. Similarly, in the instant application, it is well known in the art how to make nucleic acids which have at least 95% sequence identity to the disclosed sequences, and the specification discloses how to test to determine if the sequence is differentially expressed in melanoma. Like Example 14, the genus of nucleic acids that have at least 95% or 99% sequence identity to the disclosed

sequences will not have substantial variation since all of the variants must have the same expression in certain tumors.

Furthermore, while Applicants appreciate that actions taken by the PTO in other applications are not binding with respect to the examination of the present application, Applicants note that the PTO has issued many patents containing claims to variant nucleic acids or variant proteins where the applicants did not actually make such nucleic acids or proteins. Representative patents include U.S. Patent No. 6,737,522, U.S. Patent No. 6,395,306, U.S. Patent No. 6,025,156, U.S. Patent No. 6,645,499, U.S. Patent No. 6,498,235, and U.S. Patent No. 6,730,502, which are attached hereto as Exhibits 13-18.

In conclusion, Applicants submit that they have satisfied the written description requirement for the pending claims based on the actual reduction to practice of SEQ ID NO: 51, by specifying the high stringency conditions under which hybridization occurs, and by describing the gene expression assay, all of which result in a lack of substantial variability in the species falling within the scope of the instant claims. Applicants submit that this disclosure would allow one of skill in the art to "recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus." Hence, Applicants respectfully request that the PTO reconsider and withdraw the written description rejection under 35 U.S.C. §112.

Rejections Under 35 U.S.C. §102(e)

Claims 1-8, 11-14 and 16-20 were rejected under 35 U.S.C. 102(e) as being anticipated by Baker et al. (WO 01/64888, published September 20, 2001 with priority to December 1, 2000). As discussed in the Amendment and Response to Office Action submitted October 1, 2004, the present application claims priority to U.S. Provisional Patent Application Serial No. 60/099812, filed Sept 10, 1998 while the earliest priority date of the cited PCT application is March 1, 2000. In addition, Applicants note that both the present application and WO 01/68848A2 claim priority to PCT/US00/14042 and PCT/US00/23328. Accordingly, Applicants maintain that in view of the foregoing, the cited PCT application is not prior art under 35 U.S.C. §102(e), since it was not filed before Applicants invention of the claimed subject matter.

Claims 1-8, 11-14 and 16-20 were rejected under 35 U.S.C. 102(e) as being anticipated by Baker et al. (US PreGrant Publication published Feb 6,2003 with an earlier filing date of

September 20, 2000 with priority to December 1, 2000) is maintained for reasons made of record in the Office Action mailed 7-2-04. As discussed in the Amendment and Response to Office Action submitted October 1, 2004, the present application claims priority to U.S. Provisional Patent Application Serial No. 60/099812, filed Sept 10, 1998 while the earliest priority date of the cited U.S. application is Sept. 16, 1998. Applicants further note that both US2003/0027275 and the present application claim priority to PCT/US99/20111, PCT/US00/14042, and PCT/US00/23328. In view of the foregoing, Applicants maintain that US2003/0027275 is not prior art under 35 U.S.C. §102(e) since it was not filed before Applicants invention of the claimed subject matter.

Objection to the Specification

The Examiner requested that the trademark American Type Culture Collection (ATCC™) be recognized wherever it appears. Applicants have amended the specification in accordance with this request.

Rejections Under 35 U.S.C. §112-Deposit

Claims 1, 2, 3,4,5,6,13,14 and 16-20 were rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The Examiner asserts that the referral to the deposit on page 123 is an insufficient assurance that all required deposits have been made and all the conditions of 37 CFR 1.801-1.809 have been met. The Examiner requests that Applicants provide assurances that all restrictions upon pubic access to the ATCC™ accession number 203245 as specifically claimed, will be "irrevocably removed upon the grant of a patent from this application" specifically using this exact language.

Applicants provide a statement containing the requested language herewith.

Rejections Under 35 U.S.C. §102(b)

Claims 1-8, 11-14 and 16-20 were rejected under 35 U.S.C. 102(b) as being anticipated by Ashkenazi et al. (WO 00/77037, published May 22, 2000). The Examiner asserts that Ashkenazi et al. teach a nucleic acid encoding a polypeptide and a polypeptide lacking its signal peptide that is identical as compared with the polypeptide set forth in SEQ ID NO:52. SEQ ID NO:52 is identical as compared with SEQ ID NO:106 in Ashkenazi et al. and encodes the PR01411 polypeptide (see page 29, description for Figures 53 and 54). The Examiner also maintains that Ashkenazi et al. contemplate fusion proteins including immunoglobulin fusion

proteins with the PRO polypeptides (see pages 75-76). The Examiner states that Ashkenazi et al. contemplate portions of the PRO polypeptides (pages 71-72 (lines 12-15 in particular) and page 76, lines 5-15).

The Examiner asserts that Ashkenazi (WO 00/77037) was published May 22, 2000. However, Ashkenazi (WO 00/77037) was filed on May 22, 2000 but was not published until December 21, 2000.

As discussed above, Applicants maintain that the present application is entitled to priority date of 9/10/1998 and the data in Example 18 (Tumor Versus Normal Differential Tissue Expression Distribution), relied on in part for the utility of the claimed polynucleotides, were first disclosed in PCT Application PCT/US00/23328 filed 8/24/2000, on page 93, line 3, through page 96, line 35. As the December 21, 2000 publication date of Ashkenazi is not more than one year before either 9/10/98 or 8/24/2000, Applicants maintain that Ashkenazi (WO 00/77037) is not prior art under 35 U.S.C. §102(b).

Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. §102(b) be withdrawn.

CONCLUSION

In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: March 16, 2005

By: _____
Daniel Hart
Registration No. 40,637
Attorney of Record
Customer No. 30,313
(619) 235-8550

1337128_1 - 031305